Treatment of the Overactive Bladder: Where We Stand in 2003

Roger R. Dmochowski, MD, FACS

Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN

The understanding and management of overactive bladder (OAB) continue to evolve. However, argument persists as to the exact incidence of the disease and the underlying pathophysiology of the symptom complex. Individual differences in symptomatic impact and, more importantly, personal coping partially account for the disparity noted among demographic estimates currently extant. Likewise, the underlying pathophysiology that leads to overt OAB syndrome is, as yet, incompletely characterized. Muscarinic receptor behavior provides partial explanation, but other complex underlying receptor and neurotransmitter interactions probably are also a component of the presentation. Current state-of-the-art therapy relies on an exclusionary diagnosis prior to the inception of therapy. Ideally, optimal therapy involves behavioral and pharmacologic interventions combined to maximize therapeutic results. Antimuscarinic therapy provides only a degree of relief from the bothersome symptoms of OAB. As yet, few options exist for patients who have previously failed oral antimuscarinic intervention. Herein, the evolving OAB landscape will be considered as it currently stands in 2003. The current lack of optimal symptom control will most assuredly lead to the development of new pathways for OAB treatment.

[Rev Urol. *2003;5(suppl 8):S11-S17*]

Key words: Overactive bladder • Muscarinic receptors • Oxybutynin • Tolterodine

The syndrome of urinary urgency, urge urinary incontinence, and urinary frequency known as the overactive bladder (OAB) continues to evolve from the standpoint of the known impact of the disease, which is defined as the number of persons affected and how those persons respond to the symptomatic bother associated with the complex. Exact estimates of impacted persons vary

widely and probably do not reflect the true population impact of the syndrome. Clearly, there is heterogeneity in individual behavior associated with the impact of OAB. This variability in human response affects not only self identification but also ultimate therapeutic benefit, as behavioral modification and adherence to this modification are a significant component of the overall management of this symptom complex.

The underlying pathophysiology of OAB is, as yet, incompletely elucidated. In the past, the entire management scenario of OAB had been dependent on modulation of muscarinic receptors. These receptors, although important to intrinsic detrusor function, do not appear to be completely responsible for OAB, given the incomplete therapeutic responses obtained with current agents. Further investigation into new receptor groups and alternative neurotransmitters may provide a more complete definition of the component pathophysiologic entities contributing to OAB.

To date, treatment of OAB has been constituted on a combination of behavioral and pharmacologic therapies. These entities produce a magnitude of effect that, although beneficial for the majority of patients, is far from curative. Concepts of therapeutic benefit and the evaluation of benefits continue to evolve; however, we currently cannot predict which symptomatic vignette will respond most effectively to our interventions.

Demographics

OAB is not a syndrome of constancy; in fact, there is marked variability of presentation among affected persons. Characterization of the typical patient with OAB is problematic because relatively few patients seek therapy for their symptoms. It is estimated that 1.5 million patients are currently receiving active pharmacologic therapy for OAB,[1] yet estimates of disease prevalence reflect much higher symptomatic permeation. Older estimates of prevalence reflect an overall affected population of 17 million.[2] More recent estimates are much higher: postal survey estimates of US prevalence currently approach 33 million.[3]

Characterization of the typical patient with OAB is problematic because relatively few patients seek therapy for their symptoms.

Milsom and colleagues[3] assessed 16,776 persons in 6 European countries using telephone or direct-interview techniques. Participants were surveyed as to whether they experienced symptoms of OAB; whether they had sought medical advice; and, if so, what therapy had been rendered. In persons aged 40 years or older, the overall prevalence of OAB was found to be 16.6%, with the predominant symptom being frequency (85%), followed by urgency (54%) and urge incontinence (36%). Urinary urgency and frequency was the most common combined symptomatic presentation (74%). Overall, 79% of respondents who reported OAB symptoms had experienced the symptoms for 12 months or more, with 49% noting symptomatic bother for 3 years or more. Only urge incontinence was more prevalent in women; prevalences of frequency and isolated urgency were roughly equal between the sexes.[3] These results stand in comparison to those from pooled studies, which show marked variability, in large part due to differing definitions of OAB.[4]

Analysis of a subset of the study group (n = 1916) indicated that 60% of subjects with OAB symptoms had reported their symptoms to a physician. Of that group, 27% were currently receiving medication for the condition and an additional 27% had tried but failed medication. Of interest, 65% of the patients who had failed therapy would seek physician assistance at a later time. Sixty-two percent of patients had used coping strategies to control their voiding dysfunction (fluid restriction and toilet mapping), but only 47% were using these methods at the time of the assessment. Essentially equal proportions of men and women (65% and 67%, respectively) reported that their symptoms had an effect on daily living.[3]

The authors calculated the overall prevalence of OAB in the countries assessed (France, Germany, Italy, Spain, Sweden, and the United Kingdom) to be 22.18 million. When analyzing symptom prevalence by decade, the authors noted roughly equal distribution between the sexes (overall: men, 15.6 %; women, 17.4%), with symptoms increasing in prevalence through the eighth decade of life. The impact of frequency and urgency on health care–seeking behavior was noted to be as great as that of urge incontinence (59% vs 66%, respectively).[3]

The impact of frequency and urgency on health care–seeking behavior was noted to be as great as that of urge incontinence (59% vs 66%, respectively).

Several findings from this trial are pertinent to the population impact of OAB in 2003. OAB is not a disease of aging (43% of respondents were

younger than 65 years), although the amplification with aging cannot be ignored. The significant number of men responding affirmatively must be viewed in light of the concurrent development of symptoms arising from benign prostatic hyperplasia, a diagnostic entity not identifiable to the patient. Therefore, the actual prevalence in men may be less than was reported. In addition, the impact of voiding dysfunction (urgency and frequency) apart from incontinence is overtly apparent from this analysis.

The disparity noted above is partially emblematic of the fact that, although many patients may identify personal symptoms of OAB, the level of bother of these symptoms is variable for each affected person. Although not well elucidated, it would seem that some persons are not bothered by what would be considered a significant magnitude of symptoms (eg, frequency and incontinence). Other patients are tremendously troubled by a minimal level of symptoms. The overt conclusion is that, although the raw incidence numbers for patients identifying themselves as suffering with OAB are substantive, the majority of these sufferers are not impacted enough to seek medical care (either due to a lesser magnitude of symptom presence or less self-perceived bother). Therefore, as we recognize that behavioral intervention is needed to optimize therapy for OAB (see below), we must also realize that behavior (influenced by factors inclusive of embarrassment and other more imperceptible issues) substantively affects overall demographic estimates—for overall incidence as well as care-seeking behaviors.

Pathophysiology

The foundation for pharmacologic therapy for OAB has heretofore been based on antimuscarinic agents. The use of these agents has been promulgated on the concept that OAB is primarily caused by muscarinic receptor dysfunction. Pharmacologic therapy has focused on muscarinic (specifically M_3) receptor behavior. However, an expanding knowledge base has proved this premise to be overly simplistic. Indeed, the seeming "anticholinergic therapeutic ceiling" provides clinical evidence further underscoring the incomplete nature of the focused muscarinic therapeutic premise.

Nitric oxide appears to modulate low detrusor pressure during micturition and probably serves to facilitate vesical storage function.

From the standpoint of receptor behavior, the bladder represents a heterogeneous organ. The bladder dome possesses the highest density of muscarinic receptors,[5] with the M_3 receptor being predominant. Long appreciated as being present in the bladder body, ß-adrenergic receptors, which have been known to be involved with detrusor relaxation, have recently been noted to have a more significant role in the detrusor dysfunction associated with bladder outlet obstruction. In normal circumstances, release of acetylcholine in the dome produces bladder contraction.[6] Nitric oxide appears to modulate low detrusor pressure during micturition and probably serves to facilitate vesical storage function.

There appears to be some variability in muscarinic subtype makeup of the detrusor among persons and between the sexes. However, only the M_2 and M_3 receptors may be clinically significant for detrusor contraction. The M_3 receptor is considered to be primarily responsible for detrusor contraction; however, the M_2 receptor is present in a higher density than the M_3, by approximately 3 to 1 in humans, a finding that has also been noted in all other mammals.[7] Although as yet unspecified in humans, the M_2 receptor may play an important role in pathologic states. Muscarinic receptors are collocated on both parasympathetic and sympathetic nerve endings, regulating acetylcholine and noradrenaline release. Presynaptic muscarinic receptors in the detrusor both inhibit and facilitate detrusor function.

M_1 receptors may also be present at pre-junctional sites on cholinergic nerve terminals in the bladder and are facilitatory for bladder contraction.[8] M_1 receptors appear to facilitate acetylcholine release during phasic high-amplitude nerve activity, such as voiding.[9] In contrast, inhibition of these receptors results in a reduction in the release of neurotransmitters. The role of adenyl cyclase in instigating receptor responsiveness has yet to be defined but seems to be associated with muscarinic receptor behavior. Adenyl cyclase may serve as the facilitatory entity for muscarinic receptors.

The OAB syndrome likely results from a disorder at multiple sites within the detrusor.

Despite our increasing knowledge base, the exact mechanism of normal and abnormal detrusor function remains undefined. The OAB syndrome likely results from a disorder at multiple sites within the detrusor. Recent identification of purinergic

receptors within the detrusor associated with normal detrusor activity and, conversely, the loss of these receptors in certain detrusor overactivity states, may indicate a significant role for this receptor family as underlying the pathophysiology of OAB.

Although not yet defined, the roles of the other muscarinic receptor subtypes (ie, M_1, M_4, M_5) in OAB may prove important—if not as sites of therapeutic potential, then possibly as sites modulating side effects associated with anticholinergic drugs. Although several muscarinic receptor subtypes (including M_1 and M_5) play a role in in-vivo responses in rodent salivary glands, M_3 is the most important receptor and its modulation accounts for some of the xerostomia associated with the use of anticholinergic drugs. Likewise, vascular and cardiac M_1 and M_2 receptors are responsible for smooth muscle relaxation as well as cardiac rhythm (atrioventricular node). Although of minimal clinical impact, these receptors can produce adverse events of consequence for some persons.

All 5 subtypes of muscarinic receptors are widely distributed throughout the central nervous system (CNS). The variable location and differing responses associated with stimulation of receptors in these locations indicate that anticholinergic agents that can enter the CNS may produce a variety of effects, dependent on the degree of blood brain barrier penetration, molecular size, and overall electrostatic charge. Given the presence of all receptor subtypes in a generalized distribution, it is unlikely that any anticholinergic agent could be without risk of CNS adverse events, unless no penetration into the CNS occurred.

Much interest and attention has been focused on putative afferent mechanisms and their interaction with detrusor function and disorder. The vanilloid receptor family, with their role in unmyelinated nerve (C-fiber) activity in pathophysiologic detrusor states, has been identified as potentially contributory. However, the possibility exists that other afferent mechanisms may contribute to normal or abnormal detrusor function. The ultimate role of these receptors and/or transmitters will likely be identified as a component disorder within the larger framework of OAB. This field of investigation may also provide the basis for combined pharmacotherapy, using standard anticholinergic agents plus as yet unspecified pharmacologic entities to further boost symptomatic response (much as with incremental antihypertensive drug therapy).

All 5 subtypes of muscarinic receptors are widely distributed throughout the central nervous system.

Therapeutic Implications

The combination of behavioral therapy and pharmacologic intervention has been shown to be superior to either intervention used as an isolated entity. The effectiveness of behavioral therapy used alone has been compared with that of pharmacologic intervention. Burgio and colleagues[10] compared behavioral pelvic floor therapy for the treatment of urge urinary incontinence with oxybutynin chloride therapy or placebo. A total of 197 women aged 55 years or older were evaluated prospectively in a randomized study; primary end points were reduction in urinary incontinence episodes (by diary recording) and patient approbation of therapy and perception of improvement.

Behavioral therapy resulted in an 80.7% reduction (30% complete cure) in incontinence episodes, which was significantly superior to oxybutynin (68.5% reduction, 23% completely continent) and placebo (39.4% reduction). For all interventions, the greatest velocity of change occurred early in the study, with a slower rate thereafter. Patient perception of improvement was also greatest in the behavioral therapy group (74.1%) versus the drug therapy (50.9%) and placebo (26.9%) groups.[10]

To examine the possibility of further benefit with combined therapy, Burgio and colleagues[11] evaluated another population of 35 community-dwelling older women (mean age, 69.3 years) in a randomized controlled trial with a modified crossover design. Single modal behavioral therapy reduced incontinence episodes (based on diary reporting) by 57.5%. Addition of an anticholinergic agent (oxybutynin chloride, 2.5 mg, titrated on the basis of efficacy and tolerability to 5 mg 3 times daily) yielded an incremental response, improving urge incontinence reduction to 88.5% (P = .034). Similarly, isolated drug therapy produced a 72.7% reduction in incontinence episodes, which increased to an 84.3% reduction after the addition of simultaneous pelvic floor therapy. In clinical practice, however, fewer than half of patients originally

The combination of behavioral therapy and pharmacologic intervention has been shown to be superior to either intervention used as an isolated entity.

using behavioral therapy remain on this therapy chronically, another expression of the behavioral overlay of this syndrome.

Extended-release (ER) oral formulations of oxybutynin and tolterodine are now available for the treatment of OAB and provide improved compliance given their once-daily dosing requirements. However, recent studies directly comparing these 2 formulations show that the overall magnitude of response to treatment is greatly dependent on the type of testing methodology and the degree to which subjective and objective factors are used to create a composite analysis of effect.

The Overactive Bladder: Judging Effective Control and Treatment (OBJECT) study compared the efficacy and tolerability of oxybutynin chloride ER and tolterodine tartrate ER in 378 patients with up to 50 episodes of incontinence per week. Diaries were used to assess the efficacy of the medications, with outcome measures being episodes of micturition frequency, urge incontinence, and total incontinence.[12]

Oxybutynin ER was significantly more effective than tolterodine ER in reducing weekly micturition frequency, urge incontinence episodes, and total incontinence episodes. However, quality-of-life improvements were similar between the 2 treatment groups, with both showing statistically significant improvement from baseline. Therefore, the improvement in quality of life was independent of the agent used and appeared to be more reflective of the broad improvements noted in both active-treatment arms.[12]

The Antimuscarinic Clinical Effectiveness Trial (ACET) compared tolterodine ER (2 mg or 4 mg) with oxybutynin ER (5 mg or 10 mg) in a prospective, open-label, randomized trial; primary outcomes were patient and physician subjective appraisal of drug treatment at baseline and after 8 weeks of therapy (using a 3-tiered symptom response criterion scale). A visual analogue scale (0-100) was used to assess the severity of dry mouth. The active arms were equally distributed among the study population of 1289 subjects.[13]

Drug efficacy as reported by patient perception was 70% for tolterodine ER, 4 mg, compared with 60% for both tolterodine ER, 2 mg, and oxybutynin ER, 10 mg; efficacy was lowest (59%) in the group that received oxybutynin ER, 5 mg. The 4-mg tolterodine ER dose was statistically superior to all other dosing regimens, and this superiority of effect was noted independent of disease severity. Prior use of OAB drugs did not affect drug response or patient perception of drug effect. Although patient perception was a clear discriminator between interventions, no objective criteria were included for cross-referencing purposes.[13]

In clinical practice, however, fewer than half of patients originally using behavioral therapy remain on this therapy chronically.

The Overactive Bladder: Performance of Extended Release Agents (OPERA) trial included 790 women who were randomly allocated to either oxybutynin ER, 10 mg daily, or tolterodine ER, 4 mg daily, for 12 weeks. Outcome criteria were based on diary analysis, with primary end points being reductions in micturition frequency, urge incontinence episodes, and total incontinence episodes. Patients assessed adverse events with a 3-level (mild, moderate, or severe) analytic scale.[14]

Micturition frequency was the only outcome that demonstrated a statistical difference between the treatment arms, with the greater magnitude of effect associated with oxybutynin therapy. However, substantial magnitudes of effect were demonstrated in both active-treatment arms for all outcome criteria. Overall, approximately 1 of 5 patients became continent in either treatment arm (more so in the oxybutynin arm). The frequency and magnitude of adverse events were similar between the active-treatment cohorts. Again, quality of life appeared to parallel symptom improvement as opposed to the use of a particular agent.[14]

In yet another study, which compared transdermal oxybutynin (oxybutynin TDS) with oral tolterodine ER, 361 adult patients were randomized to 12 weeks of double-blind, double-dummy treatment with twice weekly oxybutynin TDS, 3.9 mg/d; tolterodine ER, 4 mg/d; or placebo. In this phase 3b analysis, both active agents significantly reduced the number of daily incontinence episodes, increased average void volume, and improved quality of life compared with placebo. Of interest, anticholinergic adverse events were most frequent during treatment with tolterodine ER, occurring in 7.3% of subjects, compared with 4.0% of those who received oxybutynin TDS and 1.7% of those who received placebo.[15]

In this trial, all patients were known prior responders to anticholinergic therapy before study entry; therefore, the rate of adverse events with tolterodine treatment was the lowest reported to date in clinical trials. However, there are clear advantages with transdermal delivery of oxybutynin compared with the immediate-release oral formulation, as demonstrated with these

results and those obtained in earlier phase 3 analysis. As in the previously mentioned trials, quality-of-life improvements were significant in both treatment arms and are reflective of the approbation of therapy conferred by even partially responding patients with OAB.[15]

Where does this information place physicians and patients as of 2003? Treatment of OAB has several confounding factors. The strong placebo response of this symptom complex (30%-45%) is reflective of the strong behavioral effect of diary record keeping, as well as the training effect of self awareness of voiding dysfunction. In this context, the term "placebo effect" actually represents the composite of any potential placebo benefit and training response.

The results of the studies by Burgio and colleagues[10,11] provide a template for analysis of behavioral therapy as an independent intervention. The behavioral effect is clearly capable of producing some response in a substantial number of persons with OAB. However, as demonstrated by Milsom and colleagues,[3] patients do not continue to use behavioral strategies long term, even when they perceive the benefit of these strategies. The qualified behavioral interaction associated with this symptom complex may, therefore, be reflective of a group of symptoms that are variable in intensity, which in turn instigate a variable bother level for each patient, who in turn reacts to the mutable scenario uniquely, dependent on individual coping strategies. Given the complexity of this symptom-behavior interaction, it is not surprising that patients are extremely variable in their compliance with treatment regimens.

Pharmacologic efficacy is best assessed through the use of composite reporting (subjective plus objective criteria) for full encapsulation of response.

Another concern when evaluating symptomatic intervention is how to best gauge response. Clearly, from the standpoint of drug registration and approval by administrative agencies, firm outcome parameters (reduction or resolution of urge incontinence and urinary frequency) are paramount to isolate drug effect for purposes of efficacy analysis. However, these identifiable and measurable diary-based criteria are only one component of drug response. Subjective approbation by the patient of drug effect (as produced by a coalescence of efficacy and tolerability—the patient's internal therapeutic index) is also crucial for determination of drug effect, especially for a disease that largely impacts quality of life. Therefore, a balance of objective and subjective responses is crucial when considering the overall drug benefit.

The concept of improvement is one that has merit for patients and one that, heretofore, has not been adequately delineated for OAB. Recent appreciation of reporting differences has amplified the importance of this concept for this symptomatic complex. These considerations are all the more important given the similar magnitudes of effect of the pharmacologic agents currently being used. Therefore, pharmacologic efficacy is best assessed through the use of composite reporting (subjective plus objective criteria) for full encapsulation of response.

The most recent debate regarding drug efficacy has focused on how best to measure improvement in urinary urgency as an isolated symptom. As no objective criteria exist, the concept of magnitude scoring using visual analog scales or other ordered ordinal scales has been proposed as the

Main Points

- Few patients with overactive bladder (OAB) seek therapy for their symptoms. It is estimated that 1.5 million patients are currently receiving active pharmacologic therapy for OAB, yet estimates of disease prevalence reflect much higher symptomatic permeation. Postal survey estimates of US prevalence currently approach 33 million.
- Until recently, OAB was believed to be primarily caused by muscarinic receptor dysfunction, and treatment, therefore, has been based on antimuscarinic agents. However, an expanding knowledge base has proved this concept of OAB to be overly simplistic. More research is needed to fully understand the pathophysiology of this symptom complex.
- The combination of behavioral therapy and pharmacologic intervention for the treatment of OAB has been shown to be superior to either intervention used alone. In a study by Burgio and colleagues, single modal behavioral therapy reduced incontinence episodes by 57.5%. Addition of an anticholinergic agent (oxybutynin) yielded an incremental response, improving urge-incontinence reduction to 88.5% (P = .034).
- Extended-release oral formulations of oxybutynin and tolterodine are now available for the treatment of OAB and provide improved compliance given their once-daily dosing requirements.

best method with which to quantitate symptomatic response (similar to methods used for assessing improvement in subjective pain). Although concept and validity testing of these scales is in progress, it is evident that reporting of symptomatic change will soon include an analysis of urge response as part of overall pharmacologic effect.

Conclusion

The analysis of OAB continues to progress, with further incremental knowledge regarding disease effect being made on both population and individual bases. The realization of the symptomatic burden of OAB has produced better analytic testing of disease and therapeutic effect. This testing is, however, limited by the highly variable presentation of and response to the OAB complex.

There are currently limitations to providing optimal therapy for OAB, most of which involve our lack of knowledge regarding the primary pathophysiology that underpins this clinical presentation. Future advances in the understanding of this symptom complex may allow more dramatic impact to be made on the presenting symptoms of OAB. ■

References

1. IMS National Prescription Audit [database]. Fairfield, Conn: IMS Health; 2003.
2. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20:327-336.
3. Milsom I, Abrams P, Cardozo L, et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int*. 2001;87:760-766.
4. Hampel C, Wienhold D, Benken N, et al. Definition of overactive bladder and epidemiology of urinary incontinence. *Urology*. 1997;50(6A suppl):4-14.
5. Saito M, Nakamura I, Miyagawa I. Autoradiographic localization of muscarinic receptors in diabetic rat bladder [in Japanese]. *Nippon Hinyokika Gakkai Zasshi*. 1997; 88:858-867.
6. Nagahama K, Tsujii T, Morita T, et al. Differences between proximal and distal portions of the male rabbit posterior urethra in the physiological role of muscarinic cholinergic receptors. *Br J Pharmacol*. 1998;124:1175-1180.
7. Chess-Williams R. Muscarinic receptors of the urinary bladder: detrusor, urothelial and prejunctional. *Auton Autacoid Pharmacol*. 2002; 22:133-145.
8. Somogyi GT, de Groat WC. Function, signal transduction mechanisms and plasticity of presynaptic muscarinic receptors in the urinary bladder. *Life Sci*. 1999;64:411-418.
9. Yoshimura N, Chancellor MB. Current and future pharmacological treatment for overactive bladder. *J Urol*. 2002;168:1897-1913.
10. Burgio KL, Locher JL, Goode PS, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. *JAMA*. 1998;280:1995-2000.
11. Burgio KL, Locher JL, Goode PS. Combined behavioral and drug therapy for urge incontinence in older women. *J Am Geriatr Soc*. 2000;48:370-374.
12. Appell RA, Sand P, Dmochowski R, et al, for the OBJECT Study Group. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT study. *Mayo Clin Proc*. 2001;76:358-363.
13. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the Antimuscarinic Clinical Effectiveness Trial (ACET). *Curr Med Res Opin*. 2002;18:177-184.
14. Diokno AC, Appell RA, Sand PK, et al, for the OPERA Study Group. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc*. 2003;78:687-695.
15. Dmochowski RR, Sand PK, Zinner NR, et al, for the Transdermal Oxybutynin Study Group. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology*. 2003;62:237-242.